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DISSERTATION

ON

A STUDY OF LOW DOSE SUBCUTANEOUS ADRENALINE TO PREVENT ACUTE ADVERSE REACTIONS TO ANTIVENOM SERUM IN PEOPLE BITTEN BY SNAKES.

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY OF LOW DOSE SUBCUTANEOUS ADRENALINE TO PREVENT ACUTE ADVERSE REACTIONS TO ANTIVENOM SERUM IN PEOPLE BITTEN BY SNAKES"** is the bonafide record work done by Dr.KRISHNAKUMAR.P, submitted as partial fulfillment for the requirements of M.D. Degree Examinations, General Medicine (Branch 1) to be held in March 2008.

Prof.Dr.S.MUTHUKUMARAN, M.D.
Professor and H.O.D
Department of Medicine
Thanjavur Medical College Hospital
Thanjavur.

Prof.Dr.S.PALANIYANDI, M.D.
Associate Professor of Medicine
Unit Chief M IV
Thanjavur Medical College Hospital
Thanjavur.

THE DEAN
Thanjavur Medical College
Thanjavur

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INTRODUCTION

INTRODUCTION

Antivenom serum is the most effective, if not the only effective, treatment available for management of snake bite envenomation[34]. Adverse effects of the serum are common[23] and anaphylaxis can be fatal. Increasing the safety of treatment with antivenom serum for snake bite victims is therefore a matter of high priority.

Several methods have been used to reduce acute adverse reactions to the serum. The most widely used serum is polyvalent but there is now a trend towards introduction of monovalent serum. There is no evidence however that this would result in fewer adverse effects than polyvalent antivenom serum. Immunotherapy, another treatment option is still at an early experimental stage. A small test dose of antivenom serum can be used to detect patients who may develop acute adverse reactions to antivenom. This method, however is insensitive and can give rise to anaphylaxis by itself[34 57].

Prophylactic use of hydrocortisone and antihistamines before infusion with antivenom serum is also practised. Antihistamines however counter only the effects of histamine release. Hydrocortisone takes time to act, and hence it will not be effective against acute adverse reactions that can develop almost immediately after serum

treatment, which is very often administered urgently to snake bite victims. For these reasons, it is not an established practice to give hydrocortisone or antihistamines routinely to patients with snake bite before antivenom serum treatment.

Adrenaline is the drug of choice in the treatment of anaphylaxis, and it is likely to be useful in the prevention of such acute reactions to serum. There is a general reluctance to use adrenaline because of potential side effects and lack of clear guidances on use. The only available data on use of adrenaline before treatment with antivenom serum are from a few uncontrolled retrospective studies from Australia[46]. These data suggest that adrenaline is safe and effective in reducing acute adverse reactions[36].

AIM OF THE STUDY

AIM OF THE STUDY

To assess the efficiency and safety of low dose adrenaline injected subcutaneously to prevent acute adverse reactions to polyspecific antivenom serum in patients admitted to hospital after snake bite.

REVIEW OF LITERATURE

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EPIDEMIOLOGY

Snake bite is a major public health hazard in tropical and sub-tropical countries. Patients with snake envenomation present as emergencies with significant morbidity and mortality[44]. Although the exact number of persons inflicted by snake bite is not known, it is estimated that about 2,00,000 persons are annually bitten by snakes in the country and about 15,000 of these are fatal [13 48]. According to a study by Sawai in 1974, 71% of the victims are found in the age group of 11-50 yrs and 75% of the victims were male[1]. In North India 70-80% of bites are seen in the warmer months May to October, while in a study conducted in Calicut medical college, Kerala, showed a maximum incidence in winter months (Oct-Jan) with the incidence of complications also maximum during this period[49]. The use of protective footwear, long trousers and lighting at night could reduce the incidence of snake bites. Effective rodent control would also help[43].

VENOMOUS SNAKES CLASSIFICATION

3000 species of snakes in the world of which more than 200- ranging in size from 100mm long worm snakes to 6 metre long pythons - are found in India. These predators play a major role in the maintenance

of the ecosystem[39.] Approximately 1300 species are venomous. Venomous snakes are usually defined as those which possess venom glands and specialized venom - conducting fangs, which enable them to inflict serious bites upon their victims. In general there are five families of venomous snakes recognized: the Coloubridae, which possess small rear fangs; the front-fanged Elapidae and Hydrophidae; and the viper group, which consists of the Viperidae and Crotalidae. Venomous snakes are widespread throughout the world. However they do not occur in several islands, New Zealand, Ireland, Iceland, the Azores and Canaries.

In South India the Irula tribals, over years, have been supplying millions of snake skins for export. As this trade has been banned today, they catch snakes for venom extraction and this venom is then used in the process of antivenom production[60].

SYSTEMATIC CLASSIFICATION OF VENOMOUS SNAKES IN THE WORLD

There are about 2500 to 3000 species of snakes of which about 500 belong to five families of venomous snakes, Atractdaspididae, Elapidae, Hydrophidae, Colubridae (some species) and Viperidae[55].

Family	Species	Distribution	Characteristics
Elapidae	Kraits, Cobras, Mambas, Coral snakes	Americas, Africa, Asia, Australasia	Small head, short and fixed fangs.
Viperidae	Viper snakes	Europe, Africa, Asia	Large, flattened triangular head, large grooved fangs on the maxillary bone.
Crotalidae	Rattlesnakes	Americas, Parts of Southeast Asia, Southeast Europe	Similar to the family Viperidae, but they possess heat-sensitive pits on the head
Colubridae	Tree snakes	In all parts of the world, except Australasia	Short grooved fangs at rear of upper jaws.
Hydrophidae	Sea snakes	Asia and Australasia	Nostrils dorsally on head, flattened tail.

In India, the poisonous snakes belong to three broad families:

(a) ELAPIDAE - Cobras, Kraits

(b) VIPERIDAE

(i) Viperinae - Russell's Viper, Saw-scaled Viper

(ii) Crotalinae - Pit Viper

(c) HYDROPHIDAE - Sea Snakes

The King cobra is found in the forests or their vicinity in the Himalayas, Bengal, Assam and South India. The Russell's viper is commonly found in the plains of Punjab, Maharashtra, field of Andhra and Tamil Nadu and the Brahmputra Valley. The pit viper is found in the hilly areas of Western Ghats and the Sunderbans in Bengal. The banded krait is commonly found in Assam, Bengal and parts of South Asia. Sand viper is found in Rajasthan. Kraits are usually found in pairs [27].

If the physician has a mental picture of the four common poisonous snakes it would be much easier for him to know which bite has to be given significance[27].

SNAKE VENOM

Snake venom is endowed with the most complex biochemical composition of all known poisons. The physical and chemical qualities of snake venom vary greatly not from species to species, but amongst different varieties of the same species and even from time to time in the same snake.

Snake venom contains a mixture of powerful enzymes and non-enzymatic proteins and polypeptidases. They may be in the form of enzymes like phospholipase, RNA ase, DNA ase, hyaluronidase,

acetylcholine esterase, collagenase, proteases, erepsin and sphie - oxidase, which enhance autolysis and putrefaction [28 33].

The important venom constituent effects could be seen in variable combinations :

a) PROCOAGULANT ENZYMES (Viperidae predominantly)

b) HEMORRHAGINS

c) CYTOLYTIC/NECROTIC TOXINS

d) HAEMOLYTIC TOXINS

e) MYOLYTIC ENZYMES

f) PRE SYNAPTIC NEUROTOXINS (Elapidae and some viperidae)

g) POST SYNAPTIC NEUROTOXINS (elapidae)

According to PJ Deoras the average dry weight of lyophilised venom in one bite was 0.2g from a Cobra, 0.15g from a Russell's Viper, 0.022g from a krait and 0.0046g from an Echis. [3 28 29]

A case has been recorded where the bite of a King cobra caused death in convulsions in three-quarters of an hour. [28 52].

SYMPTOMS AND SIGNS OF SNAKE BITE

EARLY SYMPTOMS AND SIGNS

Following the immediate pain of the bite, there may be increasing local pain (burning, bursting, throbbing) at the site of the bite, local swelling that gradually extends proximally up the bitten limb and tender, painful enlargement of the regional lymph nodes draining the site of the bite. However, bites by kraits, sea snakes may be virtually painless and may cause negligible local swelling. Someone who is sleeping may not even wake up when bitten by a krait and there may be no detectable fang marks or signs of local envenoming.

LOCAL SYMPTOMS AND SIGNS IN THE BITTEN PART

- fang marks
- local pain
- local bleeding
- bruising
- lymphangitis
- lymph node enlargement
- inflammation (swelling, redness, heat)
- blistering
- local infection, abscess formation
- necrosis

Local swelling is a valuable sign of viper bite to the extent that its absence excludes viper bite. Local swelling occurs rarely with the Asian Cobra bite, but is not seen with Krait or sea snake bites[2].

The bite marks are deeper in Vipers[45].

Generalised (systemic) symptoms and signs

General

- Nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, prostration

Cardiovascular (Viperidae)

- dizziness, faintness, collapse, shock, hypotension, cardiac arrhythmias, pulmonary oedema, cardiac arrest

Bleeding and clotting disorders (viperidae)

- bleeding from recent wounds (including fang marks, venepunctures etc) and from old partly-healed wounds.
- spontaneous systemic bleeding - from gums, epistaxis, bleeding into the tears, haemoptysis, haematemesis, rectal bleeding or melaena, haematuria, vaginal bleeding, bleeding into the skin (petechiae, purpura, ecchymoses) and mucosae (e.g. conjunctivae), intracranial haemorrhage, meningism from subarachnoid haemorrhage, lateralizing signs and/or coma from

cerebral haemorrhage. Commonest haemorrhagic manifestation seen in a study done by Virmani and Dutt in Jammu was haematuria while for Reid it was haemoptyis. [53 37].

Neurological (Elapidae, Russels's viper)

- Drowsiness, paraesthesiae, abnormalities of taste and smell, "heavy" eyelids, ptosis, external ophthalmoplegia, paralysis of facial muscles, difficulty in opening mouth and showing tongue and weakness of other muscles innervated by the cranial nerves, aphonia, difficulty in swallowing secretions, respiratory and generalized flaccid paralysis.

Skeletal muscle breakdown (sea snakes, Russell's viper)

- Generalised pain, stiffness and tenderness of muscles, trismus, myoglobinuria, hyperkalemia, cardiac arrest, acute renal failure.

Renal (Viperidae, sea snakes)

- Loin (lower back) pain, haematuria, haemoglobinuria, myoglobinuria, oliguria/anuria, symptoms and signs of uraemia (acidotic breathing, nausea, pleuritic chest pain etc). Ischemia (due to hypotension and DIC, nephrotoxic effect of venom, pigment nephropathy associated with rhabdomyolysis and intravascular haemolysis contribute to

the development of acute tubular necrosis, bilateral cortical necrosis and renal failure commonly seen with Russell's viper. [56]

V.S.Tembe et al on autopsy found haemorrhagic interstitial nephritis, toxic proliferative glomerulitis intracerebral haemorrhage and necrosis of the liver [21 28].

Endocrine (acute pituitary / adrenal insufficiency) (Russell's viper)

- Acute phase : shock, hypoglycaemia
- Chronic phase (months to years after the bite) : weakness, loss of secondary sexual hair, amenorrhoea, testicular atrophy, hypothyroidis, hypopituitarism etc.

LONG TERM COMPLICATIONS (SEQUELAE) OF SNAKE BITE

At the site of the bite, loss of tissue may result from sloughing or surgical debridement of necrotic areas or amputation : chronic ulceration, infection, osteomyelitis or arthritis may persist causing severe physical disability. Malignant transformation may occur in skin ulcers after a number of years.

Chronic renal failure occurs after bilateral cortical necrosis (Russell's viper bites) and chronic panhypopituitarism or diabetes insipidus after Russell's viper bites in Myanmar and South India.

Chronic neurological deficit is seen in the few patients who survive intracranial haemorrhages (Viperidae).

R.Ray and K. Bhattacharya report the case of a male, aged 45, who was bitten by a viper on his right foot. Inspite of 80cc of polyvalent antivenin serum, he developed oliguria, haemetemesis and was delirious and semi concious from the eighth to the tenth day. He had absolute anuria with raised blood urea, and was given a large amount of intravenous glucose. Later on, he recovered completely [19] [28].

Bites by cobras, king cobras, kraits or sea snakes may lead, on rare occasions, to the rapid development of life-threatening respiratory paralysis. This paralysis might be delayed by slowing down the absorption of venom from the site of the bite. The following technique is currently recommended.

PRESSURE IMMOBILIZATION METHOD.

Pressure immobilization is recommended for bites by neurotoxic elapid snakes, including sea snakes, but should not be used for viper bites because of the danger of increasing the local effects of the necrotic venom.

In a human volunteer study simulating intradermal and subcutaneous envenomation, using labeled radiotracer, immediately

wrapping an entire extremity with a rolled elastic bandage to a pressure of 50-70 mm Hg significantly delayed transit time from periphery to the systemic circulation [12 18]. The wrapping procedure, (the Sutherland Wrap) is intended to collapse lymphatics and superficial veins to retard venom uptake[12].

The pressure immobilization technique has been used for treatment of non necrotizing elapid snake bites in Australia where systemic toxicity is the major concern and transit times can be prolonged[58].

SPECIES DIAGNOSIS

If the dead snake has been brought, it can be identified. Otherwise, the species responsible can be inferred indirectly from the patient's description of the snake and the clinical syndrome of symptoms and signs. This will be important when operating under various international peace keeping missions where monospecific antivenoms are available.

INVESTIGATIONS / LABORATORY TESTS
20 minute whole blood clotting test (20 WBCT)

This very useful and informative bedside test requires very little skill and only one piece of apparatus - a new, clean, dry, glass vessel (tube or bottle)

OTHER TESTS

i. Haemoglobin concentration / haematrocrit : a transient increase indicates haemoconcentration resulting from a generalized increased in capillary permeability (e.g. in Russell's viper bite). More often, there is a decrease reflecting blood loss or, in the case of Indian and Sri Lankan Russell's viper bite, intravascular haemolysis.

ii. Platelet count : this may be decreased in victims of viper bites.

iii. White blood cell count: an early neutrophil leucocytosis is evidence of systemic envenoming from any species.

iv. Blood film : fragmented red cell ("helmet cell", schistocytes) are seen when there is microangiopathic haemolysis.

v. Plasma / serum may be pinkish or brownish if there is gross haemoglobinaemia or myoglobinaemia.

vi. Biochemical abnormalities : aminotransferases and muscle enzymes (creatine kinase, aldolase etc) will be elevated if there is severe local damage or, particularly, if there is generalized muscle damage (Sri Lankan and South Indian Russell's viper bites, sea snake bites). Mild hepatic dysfunction is reflected in slight increases in other serum

enzymes. Bilirubin is elevated following massive extravasation of blood. Creatinine, urea or blood urea nitrogen levels are raised in the renal failure of Russell's viper and saw-scaled viper bites and sea snake bites. Bicarbonate will be low in metabolic acidosis (e.g. renal failure).

vii. Arterial blood gases and pH may show evidence of respiratory failure (neurotoxic envenoming) and acidaemia (respiratory or metabolic acidosis).

viii. Desaturation : arterial oxygen desaturation can be assessed non-invasively in patients with respiratory failure or shock using a finger oximeter.

ix. Urine examination : the urine should be tested by dipsticks for blood/haemoglobin/myoglobin. Standard dipsticks do not distinguish blood, haemoglobin and myoglobin. Haemoglobin and myoglobin can be separated by immunoassays but there is no easy or reliable test. Microscopy will confirm whether there are erythrocytes in the urine. Red cell casts indicate glomerular bleeding. Massive proteinuria is an early sign of the generalized increase in capillary permeability in Russell's viper envenoming.

IMMUNODIAGNOSIS

Enzyme linked immunosorbent assay is a very important tool for studying both the epidemiological and clinical effects of snake bite in humans. In places where specific antidote venom is available against each species, if the snake is not brought along with the victim for identification, immunodetection of specific snake venom antigen in body fluids of the patient will help in management[56].

It has been proved by ELISA that effects of envenomation depend upon venom hours (i.e., blood venom level x time elapsed between bite and institution of treatment) rather than blood level of venom[17].

ELISA by detection of snake venom antibody can be used for retrospective diagnosis of envenoming in epidemiological studies[38].

ANTIVENOM TREATMENT

Antivenom is the only specific antidote to snake venom.

A most important decision in the management of a snake bite victim is whether or not to give antivenom.

Antivenom is immunoglobulin (usually the enzyme refined F (ab) 2 fragment of IgG) purified from the serum or plasma of horse or sheep that has been immunized with the venoms of one or more

species of snake. "Specific" antivenom, implies that the antivenom has been raised against the venom of the snake that has bitten the patient and that it can therefore be expected to contain specific antibody that will neutralize that particular venom. Monovalent or monospecific antivenom neutralizes the venom of only one species of snake. Polyvalent antivenom neutralizes the venoms of several different species of snakes. For example, Haffkine, Kasauli, Serum Institute of India and Bengal "polyvalent anti-snake venom serum" is raised in horses using the venoms of the four most important venomous snakes in India (Indian cobra, Naja naja; Indian krait, Bungarus caeruleus; Russell's viper, Daboia russelii; saw-scaled viper, Echis carinatus). 1 ml of polyvalent ASV in India neutralizes 0.6 mg of Cobra and Russell Viper venom and 0.45 mg of Krait and Saw scaled Viper venom. Antibodies raised against the venom of one species may have cross-neutralising activity against other venoms, usually from closely related species. This is known as paraspecific activity. For example, the manufacturers of Haffkine polyvalent anti-snake venom serum claim that this antivenom also neutralizes venoms of two Trimeresurus species (Pit vipers). Details of Indian manufacturers of ASV are attached as appx.

MANUFACTURERS OF ASV IN INDIA

1. Haffkine Bio Pharmaceutical Corporation Ltd.
   Acharya Donde Marg,, Panel, Mumbai - 400 012
   Tele : 022-4129320
   FAX : 022-4147564

2. Central Research Institute (Shimla Hills)
   Kasauli, Himachal Pradesh - 173 204
   Tele : 0179-32060
   FAX : 0179-272049

3. Serum Institute of India Ltd
   212/2 Hadapson, Pune - 411 029
   Tele : 020-672016
   FAX : 020-672040

4. Kings Institute of Preventive Medicine
   Guindy, Chennai.

5. Bengal Chemical and Pharmaceuticals
   6, Ganesh Chunder Avenue,
   Kolkata
   Tele : 033-2257697

MANAGEMENT

There are no universally accepted standards of care for many aspects of treatment[59].

INDICATION FOR ANTIVENOM

Antivenom treatment is recommended if and when a patient with proven or suspected snake bite develops one or more of the following signs.

Systemic envenoming

- Haemostatic abnormalities : spontaneous systemic bleeding, coagulopathy or thrombocytopenia
- Neurotoxic signs : (clinical)
- Cardiovascular abnormalities (clinical), abnormal ECG
- Acute renal failure : oliguria/anuria (clinical), rising blood creatinine/urea (laboratory)
- (Haemoglobin-/myoglobin-uria:) dark brown urine (clinical) urine dipsticks, other evidence of intravascular haemolysis or generalized rhabdomyolysis (muscle aches and pains, hyperkalemia) (clinical, laboratory)
- Supporting laboratory evidence of systemic envenoming

Local envenoming

- Local swelling involving more than half of the bitten limb (in the absence of a tourniquet)
- Swelling after bites on the digits (toes and especially fingers)
- Rapid extension of swelling (for example beyond the wrist or ankle within a few hours of bites on the hand or feet)
- Development of an enlarged tender lymph node draining the bitten limb.

PREDICTION OF ANTIVENOM REACTION

Skin and conjunctival "hypersensitivity" tests may reveal IgE mediated Type I hypersensitivity to horse or sheep proteins but do not predict the large majority of early (anaphylactic) or late (serum sickness type) antivenom reactions. Since they may delay treatment and can in themselves be sensitizing, these tests should not be used.

CONTRAINDICATIONS TO ANTIVENOM

There is no absolute contraindication to antivenom treatment, but patients who have reacted to horse (equine) or sheep (ovine) serum in the past (for example after treatment with equine antitetanus serum, equine or ovine antivenom) and those with a strong history

of atopic diseases (especially severe asthma) should be given antivenom only if they have signs of systemic envenoming.

PREVENTION OF ANTIVENOM REACTIONS

Recent studies have indicated that, while intramuscular promethazine is ineffective, subcutaneous epinephrine (adrenaline) (0.1% solution, adult dose 0.25 mg given immediately before the start of antivenom treatment) reduces the incidence of early antivenom reactions[34]. In asthmatic patients, prophylactic use of an inhaled adrenergic B2 agonist such as salbutamol may prevent bronchospasm.

In a study, the cutaneous and systemic signs and symptoms of immediate hypersensitivity were all effectively treated with antihistamines and epinephrine, with no adverse sequelae [12] [22]. In life threatening situations and if the Fab antivenom is not available, administration of antivenom to patients with a positive skin test or known allergy to horse serum is warranted [12] [26] [32].

ADMINISTRATION OF ANTIVENOM

- Epinephrine (adrenaline) should always be drawn up in readiness before antivenom is administered.

- ❖ Antivenom should be given by the intravenous route whenever possible.

Freeze-dried (lyophilised) antivenoms are reconstituted, usually with 10 ml of sterile water for injection per ampoule. The freeze-dried protein may be difficult to dissolve. Two methods of administration are recommended :

1. Intravenous infusion : reconstituted freeze-dried or neat liquid antivenom is diluted in approximately 5-10ml of isotonic fluid per kg body weight (i.e. 250-500 ml of isotonic saline or 5% dextrose in the case of an adult patient) and is infused at a constant rate over a period of about one hour. This method has the advantage that intravenous access is available for the emergency treatment of reaction.

2. Intravenous "push" injection : reconstituted freeze-dried antivenom or neat liquid antivenom is given by slow intravenous injection (not more than 2 ml/minute). It is economical, saving the use of intravenous fluid, giving sets, cannulae etc. It has been found there is no difference in reaction between the two methods[35].

Patients must be closely observed for at least one hour after starting intravenous antivenom administration, so that early anaphylactic antivenom reactions can be detected and treated early with epinephrine (adrenaline).

DOSE OF ANTIVENOM

Snakes inject the same dose of venom into children and adults. Children must therefore be given exactly the same dose of antivenom as adults.

Viper bites

The initial dose of ASV for Viper bites depends on clinical manifestations of envenomation

(a) Progressive local swelling - 50 ml

(b) Mild systemic envenomation or mild coagulagram abnormalities -- 100 ml

(c) Severe poisoning, rapidly progressive or overt hemolysis or coagulopathy - 150 - 200 ml

Elapid bites

Higher doses are indicated in elapid bites since the elapid venom is less antigenic and its absorption is faster. For patients presenting with neurotoxic features initial dose of ASV given is 100 ml[36]. The dose for children is the same as that for adults. The dose should be repeated after 6 hours if clotting parameters are deranged. If there are signs of severe neurotoxicity the dose may be repeated more frequently (even as early as 30 minutes) till a satisfactory response is obtained.

NEWER ANTIVENINS

A new antivenin (Crofab) has replaced the Wyeth horse serum based product. With local signs such as swelling, pain and ecchymoses but no systemic symptoms, give 4-6 vials of crotalid antivenin (Crofab) by slow intravenous drip in 250-500ml Saline. Repeated doses of 2 vials every 6 hours for upto 18 hours has been recommended. For elapid envenomation, give 1-2 vials of specific antivenin as soon as possible [11 25 31].

Thus if dose has been adequate, clotting time should be normal by 6 hrs [9 55].

There is a controversy about how long after envenomation Antivenom therapy is still effective. Carrison et al claim that it is most useful if given within 4 hrs, less if delayed for 8 hrs and doubtful if delayed after 24 hrs[41].

However Dwivedi et al have reported therapy with Antisnake venom to be beneficial even after 8 days and state that these is no fixed time limit[10].

After two preclinical trails studied, crotalidae polyvalent immune Fab (ovine), the therapeutic regimen was empirically determined to include repeat doses of 4-6 vials until "control" is obtained, followed

by regularly scheduled maintenance infusions. The manufacturer defines control as arrest of local tissue manifestations and return of coagulation parameters, platelet counts and systemic signs to normal. However select patients develop coagulopathy and thrombocytopenia that is resistant to antivenom treatment [12 40]. Some authors advocate control to mean clear improvement in haematologic parameters rather than complete normalization [12 40].

The use of a systemic severity of illness scale has demonstrated that antivenom will correct coagulopathies and thrombocytopaenia associated with envenomation from snakes native to the united states [7 12].

Recurrent neurotoxic envenoming after treatment of cobra bite has also been described.

CRITERIA FOR REPEATING THE INITIAL DOSE OF ANTIVENOM

Criteria for giving more antivenom

* Persistence or recurrence of blood incoagulability after 6 hr.

* Deteriorating neurotoxic or cardiovascular signs after 1-2 hr

Studies have shown that clotting abnormalities may reappear upto 72 hours after their apparent complete nomalization. This is attributed to delayed venom absorption from site of bite [11].

If the blood remains incoagulable six hours after the initial dose of antivenom, the same dose should be repeated. This is based on the observation that, if a large dose of antivenom (more than enough to neutralise the venom procoagulant enzymes) is given initially, the time taken for the liver to restore coagulable levels of fibrinogen and other clotting factors is 3-9 (mean 6) hours.

In patients who continue to bleed briskly, the dose of antivenom should be repeated within 1-2 hours.

In case of deteriorating neurotoxicity or cardiovascular signs, the initial dose of antivenom should be repeated after 1-2 hours, and full supportive treatment must be considered.

ANTIVENOM REACTIONS

A proportion of patients, usually more than 20% develop a reaction either early (within a few hours) or late (5 days or more) after being given antivenom.

Incidence of anaphylactic / oid reaction -23.56% for polyvalent antivenin (crotalidae), 14% for Crofab. Incidence of delayed serum sickness - 18-86% for the former and 16% for the latter[30]. There are three types of anaphylactoid reactions-early anaphylactoid, pyrogenic and late[30].

EARLY ANAPHYLACTIC REACTIONS

Usually within 10-180 minutes of starting antivenom, the patient begins to itch (often over the scalp) and develops urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhea and tachycardia. A minority of these patients may develop severe life-threatening anaphylaxis : hypotension, bronchospasm and angio-oedema. Fatal reactions have probably been under-reported as death after snake bite is usually attributed to the venom.

In most cases, these reactions are not truly "allergic". They are not IgE-mediated type I hypersensitivity reactions to horse or sheep proteins as there is no evidence of specific IgE, either by skin testing or radioallergosorbent tests (RAST). Complement activation by IgG aggregates or residual Fc fragments or direct stimulation of mast cells or basophils by antivenom protein are more likely mechanisms for these reactions.

PYROGENIC (ENDOTOXIN) REACTIONS

Usually develop 1-2 hours after treatment. Symptoms include shaking chills (rigors), fever, vasodilatation and a fall in blood pressure. Febrile convulsions may be precipitated in children. These reactions are caused by pyrogen contamination during the manufacturing process. They are commonly reported.

LATE (SERUM SICKNESS TYPE) REACTION :

Develop 1-12 (mean 7) days after treatment . Clinical features include fever, nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis and rarely encephalopathy. Patients who suffer early reactions and are tested with adrenaline, antihistamines and corticosteroids are less likely to develop late reactions.

TREATMENT OF EARLY ANAPHYLACTIC AND PYROGENIC ANTIVENOM REACTIONS

At the earliest sign of a reaction

- ❖ Antivenom administration must be temporarily suspended.

- Epinephrine (adrenaline) (0.1% solution, 1 in 1000, 1 mg/ml) is the effective treatment for early anaphylactic and pyrogenic antivenom reactions.

Epinephrine (adrenaline) is given subcutaneously if mild in an initial dose of 0.5 mg for adults, 0.01 mg/kg body weight for children. Severe, life threatening anaphylaxis can evolve very rapidly and so epinephrine (adrenaline) should be given intravenously at the very first sign of a severe reaction, even when only a few spots of urticaria have appeared or at the start of itching, tachycardia or restlessness. The dose can be repeated every 5-10 minutes if the patient's condition is deteriorating.

ADDITIONAL TREATMENT

After epinephrine (adrenaline), an anti-H1 antihistamine such as chloropheniramine maleate (adults 10 mg, children 0.2 mg/kg intravenous injection over a few minutes) should be given followed by intravenous hydrocortisone (adults 100 mg, children 2 mg/kg body weight). H 2 blockers may also be used but after H1 blockade. The corticosteroid is unlikely to act for several hours, but may prevent recurrent anaphylaxis.

In pyrogenic reactions the patient must also be cooled physically and with antipyretics (for example paracetamol by mouth or suppository). Intravenous fluids should be given to correct hypovolaemia.

SUPPORTIVE TREATMENT

Tetanus prophylaxis

Antibiotics

Surgical debridement of dead tissue/amputation

Fasciotomy for intracompartment syndromes.

Patients with respiratory paralysis should be given IV neostigmine 0.5 mg slow IV with IV atropine 0.6 mg 1/2 hrly for 5 doses and repeated thereafter at increasing intervals if required. Endotracheal intubation and artificial ventilation may be needed.

Steroids are advocated in both patients presenting with bleeding tendencies and with neurological manifestations. (Hydrocortisone 50 to 100 mg 1. V 8th hrly) However its use remain controversial [14].

Treatment of DIC : In a situation of viper bite the manifestations of primary fibrinolysis and DIC are reversible by administration of ASV. However, if a person has severe bleeding manifestations despite ASV administration, fresh frozen plasma,

cryoprecipitate and platelet concentrates can be given. If these blood constituents are not available fresh blood can be transfused.

Some studies show that if heparin 10,000 units is given intravenously stat followed by 5000 units 8th hrly IV and continued for 48 hrs, it is useful in the prevention of DIC. Yet other studies have shown it to be ineffective and worsening bleeding[42].

Conservative treatment when no antivenom is available

This will be the situation in many parts of the regions, where supplies of antivenom run out or where the bite is known to have been inflicted by a species against whose venom there is no available specific antivenom : for example for bites by the Malayan krait (Bungarus candidus), coral snakes (genera Calliophis and Maticora), sea snakes, the mangrove/shore pit viper (T purpureomaculatus) and the mountain pit viper (Ovophis monticola).

RECENT ADVANCES

(a) purification of IgG by immunosorbent affinity chromatography have yielded purified polyvalent antibodies with high affinity for crotalid venom. This belongs to a subclass of equine IgG called IgG (T)

(b) F (ab) fragments of IgG using papain digestion are also being studied. These retain the affinity for the venom of the large IgG molecules. They also enhance the renal clearance of the venom molecules and are less immunogenic than the whole antibody.

(c) Antisnake vaccines are also under trial at the Tropical School of Medicine, Kolkata. These newer treatment modalities are still in the experimental stages and need to be developed further before use in clinical practice.

SNAKE BITE : CAUSES OF HYPOTENSION AND SHOCK

Anaphylaxis

Vasodilatation

Cardiotoxicity

Hypovolaemia

Antivenom reaction

Respiratory failure

Acute pituitary and adrenal insufficiency

Septicaemia

EPINEPHRINE

Epinephrine (adrenaline) is a potent stimulant of both α and β adrenergic receptors and its effects on target organs are thus complex[20]. The peripheral actions of adrenaline in most tissues has been clearly differentiated into those mediated by α or β receptors depending on the predominant receptor type present in a given tissue.

Adr - $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action [51]

Administration and Preparation :

Adrenaline (epinephrine) 0.2 - 0.5 mg S.C, 1.M, .5% by aerosol ; action lasts 1/2 to 2 hrs[51].

ADVERSE EFFECTS AND CONTRAINDICATIONS :

1. Transient restlessness, palpitation, anxiety, tremor, pallor may occur after s. c / i.m injection of adrenaline.
2. Marked rise in BP leading to cerebral haemorrhage, ventricular tachycardia / fibrillation are the hazards of large doses of inadvertant IV injection.
3. Adrenaline is contraindicated in hypertension, hyperthyroidism and angina pectoris.

It should not be given during anaesthesia with halothane (risk of arrhythmia) and to patients receiving β blockers, marked rise in BP can occur[51] .

Use of epinephrine

Anaphylaxis

glaucoma

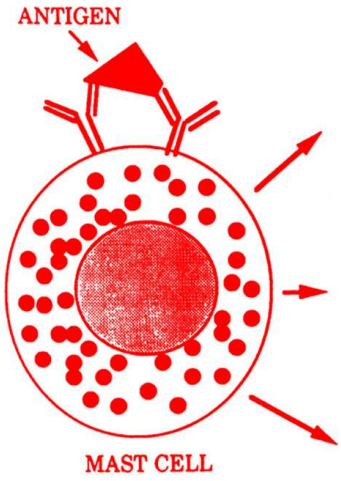
Asthma & to cause vasoconstriction [5]

HYPER SENSITIVITY REACTIONS

Hyper sensitivity reactions have been classified traditionally in to immediate and delayed types, based on the time required for a sensitized host to develop clinical reactions on re exposure to the antigen. Anaphylaxis comes under immediate hypersensitivity. (B cell or antibody mediated) [4]. The biologically active molecules that are responsible for the manifestations of Type I hypersensitivity are stored within mast cells and basophil granules and are synthesized after cell triggering. The signal for the release or production of these molecules is the cross linking of surface bound IgE by antigen [8].

6

TYPE I: IMMEDIATE HYPERSENSITIVITY (IgE-MEDIATED)



PREFORMED INTRAGRANULAR MEDIATORS

- Histamine
- Proteinases
  - Chymases
  - Tryptases
  - Carboxypeptidase
  - Cathespin G-like proteinase
- Acid hydrolases
  - β-hexosaminidase
  - β-glucuronidase
  - β–D-galactosidase
  - Arylsulfatase A
- Proteoglycans
  - Heparin
  - Chondroitin sulfate E

NEWLY FORMED MEDIATORS

- Arachidonic acid metabolites
  - Prostaglandins
  - Leukotrienes
  - Platelet activating factor
  - Thromboxanes
  - 5-, 12-HETEs (hydroxy-eicosatetraenoic acids)
- Free radicals
  - NO (nitric oxide)
  - Superoxide anion
  - Hydrogen peroxide
  - Hydroxyl radicals

CYTOKINES

- TNF-α and TNF-β
- IL-1,2,3,4,5,6,8
- GM-CSF
- IFNγ
- NGF
- Macrophage Inflammatory Protein (MIP)-2
- Basic Fibroblast Growth Factor (bFGF)
- Leukemia Inhibitory Factor (LIF)

Classification of allergic reactions (Gell and Coombs).

MATERIALS AND METHODS

MATERIALS AND METHODS

DESIGN

Prospective, single blind, randomised, placebo controlled trial.

SETTING

Thanjavur Medical College Hospital during the period of July 2007 to September 2007. (Rice paddy harvesting season, when there is a high admission rate for snake bite). 188 pts were admitted during this period. 88 of them were excluded according to the exclusion criteria.

SUBJECTS

Hundred patients with signs of envenomation after snake bite randomized to receive either adrenaline (study group) or placebo (controls) immediately before infusion of antivenom serum.

INTERVENTIONS

Adrenaline 0.25 ml (1 : 1000)

MAIN OUTCOME MEASURES

Development of acute adverse reactions to serum and side effects attributable to adrenaline.

METHODS

Consecutive patients not having exclusion criteria who were admitted after a snake bite and required antivenom serum because of systemic envenomation received either adrenaline (study group) or identical appearing placebo (controls) as pretreatment.

Patients were excluded from the study if they were pregnant, aged under 12 or over 70 years, said they had received antisera, including antivenom serum, in the past; had known adverse reactions to adrenaline, atopy, wheezing, hypertension, ischaemic heart disease, transient ischaemic attacks, strokes or unexplained focal neurological signs or had received any treatment other than first aid before admission. Patients were also excluded if electrocardiography on admission showed ischaemic changes or arrhythmias. Written informed consent was obtained from all participating patients.

TREATMENT AND FOLLOW UP

All patients were given 0.25 ml of 1:1000 adrenaline or placebo injected subcutaneously in to the forearm immediately before infusion with antivenom. Placebo consisted of 0.9% sodium chloride. Adrenaline and placebo were drawn into 1 ml "insulin" syringes which were stored in closed rigiform containers and refrigerated at 4^0C. No test doses of antivenom was used and neither

hydrocortisone nor promethazine were given as pretreatment. Patients were monitored for development of acute adverse reactions to the serum and the test drug. Pulse and Blood pressure (every 15 minutes) and an electrocardiogram (at least once within 30 minutes of being given the test drug and whenever clinically indicated) were monitored during infusion of antivenom and for one hour thereafter.

Neurological evaluations were done at the beginning and end of the infusion and whenever relevant during the observation period. Patients who received antivenom serum were kept in hospital for atleast 96 hours after the infusion.

Acute adverse reactions were graded as mild, moderate or severe according to the following Criteria.

Mild - pruritis, skin rash, without pruritis, mild urticaria, fever, rigors, nausea, vomiting.

Moderate- extensive urticaria, facial oedema, bronchospasm without cyanosis.

Severe- Pulmonary oedema, bronchospasm with cyanosis, stridor, shock or a reaction developed while the patient was receiving the serum or if the patient developed arrhythmias, ischaemic changes in

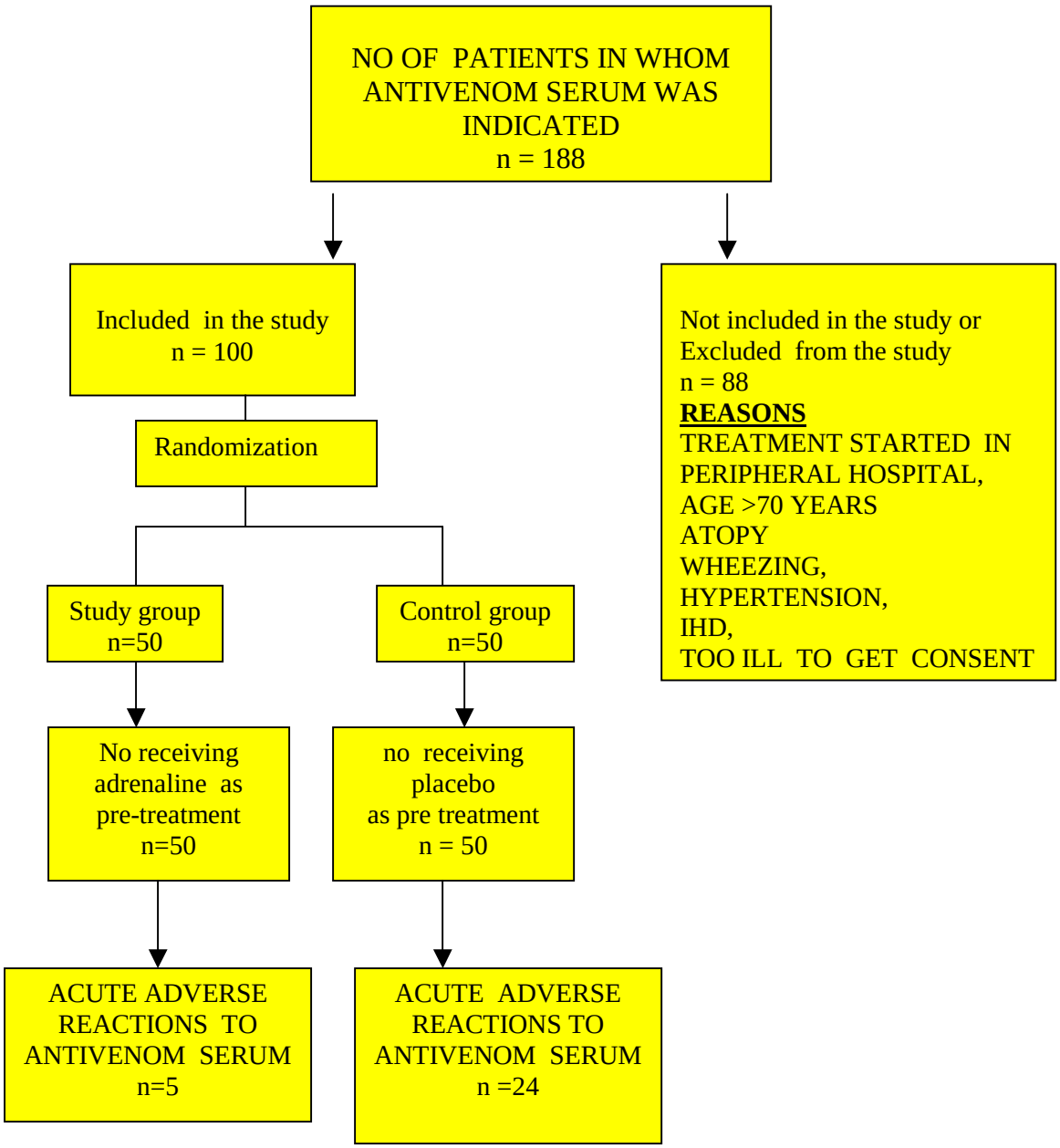
the electrocardiogram or a measurable rise in blood pressure (systolic - >20 mm Hg or Diastolic > 10 mm Hg from level before test drug was given) after the test drug and the serum, he or she was given appropriate treatment and did not take further part in the trial.

Reactions to antivenom serum were initially treated by stopping the infusion and administering 0.5ml of 1 : 1000 adrenaline intramuscularly, 200 mg hydrocortisone intravenously and 25 mg promethazine intramuscularly.

Statistical Analysis

Analysis was done using Chi square test and p value assessed.

DESIGN OF RANDOMIZED CONTROLLED TRIAL



GENERAL FEATURES

The study started in July 2007 and ended in September 2007 when hundred patients had been recruited.

Within this three month period out of a total of one hundred and eighty eight patients admitted in Thanjavur Medical College Hospital with envenomation after snake bite for whom treatment with antivenom serum was indicated, only hundred could be recruited to the study as the others had one or more exclusion criteria. Of the hundred patients recruited fifty received adrenaline and fifty received placebo. (Ten Vials) Haffkine Polyspecific antivenom serum (Haffkine Laboratories, Mumbai, India) an equine serum product were used for all patients. The serum was administered intravenously as a 200 ml infusion at fifty drops per minute over one hour. All serum used during the study was from the same batch supplied to the hospital.

CHARACTERISTICS AND DEGREE OF ENVENOMATION ON ADMISSION OF PATIENTS ACCORDING TO ALLOCATION TO PRE TREATMENT WITH ADRENALINE OR PLACEBO IN A NUTSHELL (values are numbers of patients unless stated otherwise)

DETAIL	ADRENALINE (n=50)	PLACEBO (n=50)
MALE	32	30
MEAN (SD ; RANGE) AGE (YEARS)	40.19 (13.07;19-65)	41.77 (11.6;17-65)
MEAN (SD;RANGE) WEIGHT (KG)	58.22 (4.94; 48-66)	58.17 (5.04;50-70)
SPECIES OF SNAKE *		
UNCERTAIN	22	31
RUSSELLS VIPER	18	13
COBRA	3	3
KRAIT	7	3
SYSTEMIC ENVENOMATION	48	46
COAGULOPATHY	22	30
NEUROMUSCULAR COMPLICATIONS	16	10
RENAL IMPAIRMENT	5	3
MORETHAN ONE FEATURE OF ENVENOMATION	5	3
COAGULOPATHY & RENAL	5	3
NEUROMUSCULAR & RENAL	-	-
COAGULOPATHY, NEUROMUSCULAR & RENAL	-	-
SIGNIFICANT LOCAL ENVENOMATION ONLY	6	5
SEVERE LOCAL SWELLING(#)	26	34

Swelling of more than half of bitten limb. (none had necrosis)
* species of snake mentioned only when dead snake brought to hospital.

ACUTE ADVERSE REACTIONS TO ANTIVENOM SERUM TO PATIENTS BITTEN BY SNAKES, ACCORDING TO PRE TREATMENT (ADRENALINE OR PLACEBO) - IN A NUTSHELL

DETAIL	ADRENALINE (n=50)	PLACEBO (n=50)	RELATIVE RISK	P VALUE
NO (%) OF REACTION TO SERUM	5	24	0.21	0.00005
TIMING OF ADVERSE REACTIONS TO SERUM (MIN)				
<15	4	19		
15-30	1	5		
>30	0	0		
NO (%) OF REACTIONS ACCORDING TO SEVERITY				
MILD	4	12	0.67	.03
MODERATE	1	8	.125	.01
SEVERE	0	4	0	.03

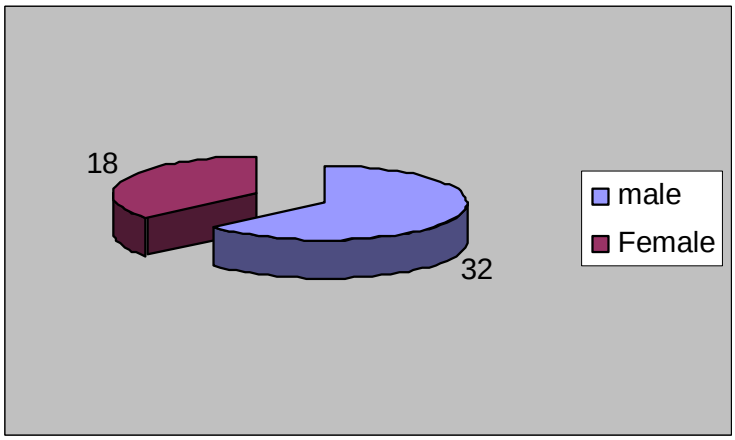
OBSERVATION

OBSERVATION

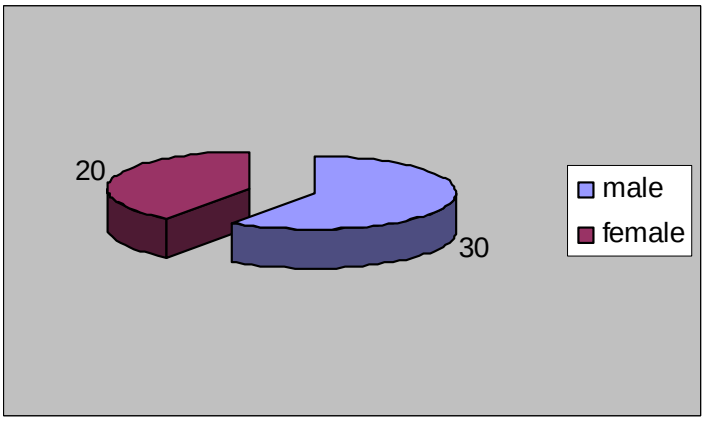
SEX DISTRIBUTION IN STUDY AND PLACEBO GROUP

DETAIL	ADRENALINE (n-50)	PLACEBO (n-50)
MALE	32	30
FEMALE	18	20

STUDY GROUP



PLACEBO GROUP

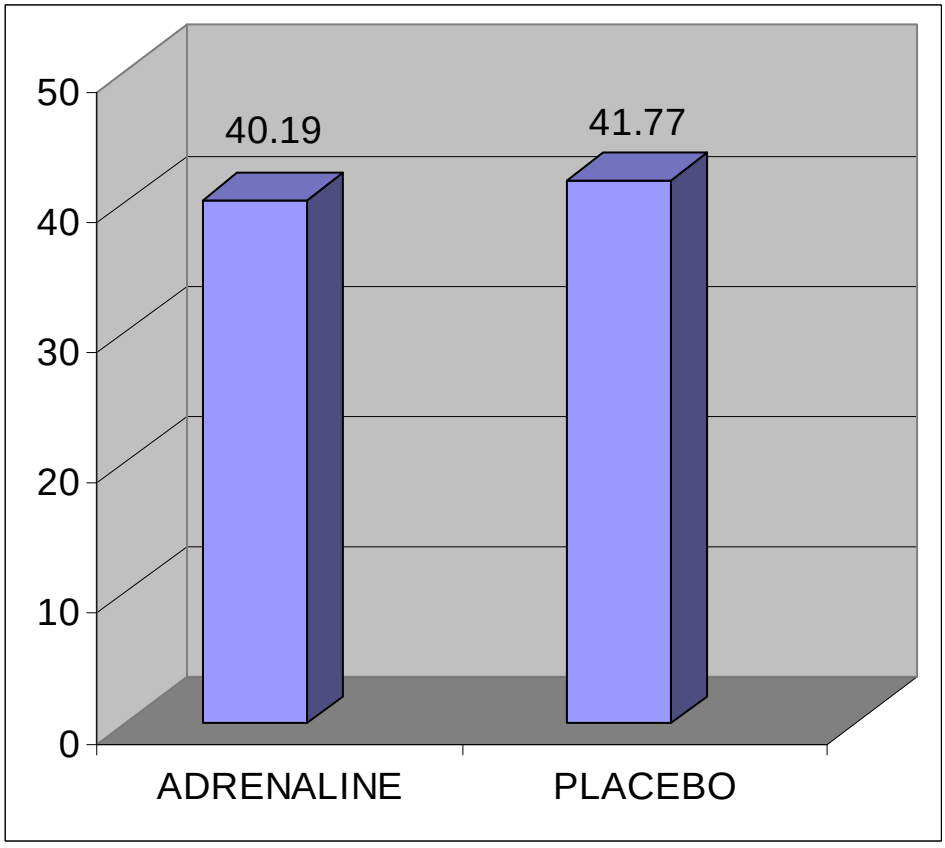


The data shows that there is no significant difference in sex distribution among study and placebo group.

MEAN AGE AMONG MEMBERS IN STUDY AND PLACEBO GROUP

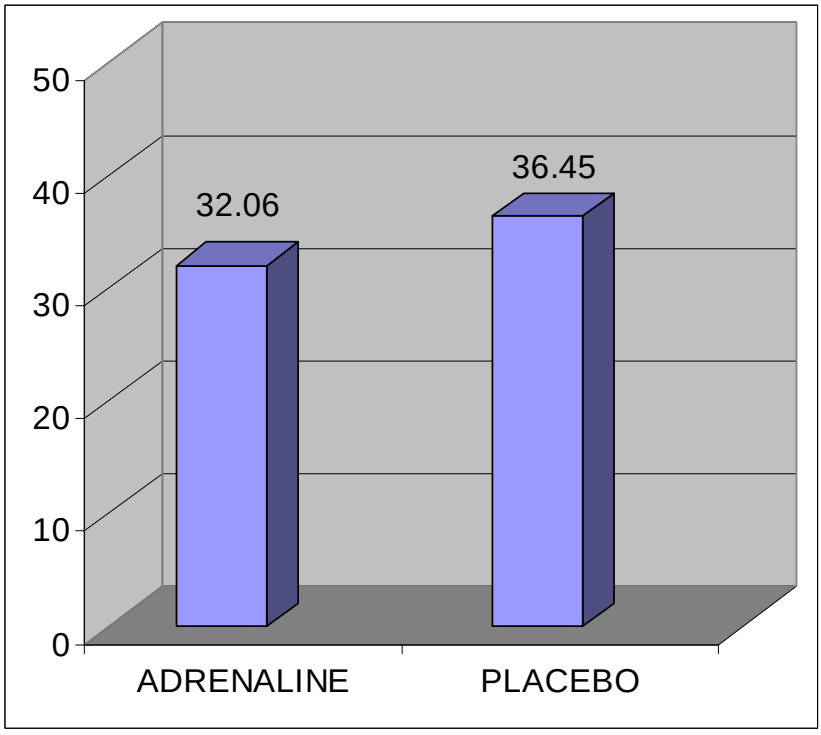
MALE

DETAIL	ADRENALINE	PLACEBO
MEAN (SD ; RANGE) AGE (YEARS)	40.19 (13.07 ; 19-65)	41.77 (11.6; 17-65)



FEMALE

DETAIL	ADRENALINE	PLACEBO
MEAN (SD; RANGE) AGE (YEARS)	32.06 (8.35 ; 19-45)	36.45(11.10 ; 14-55)

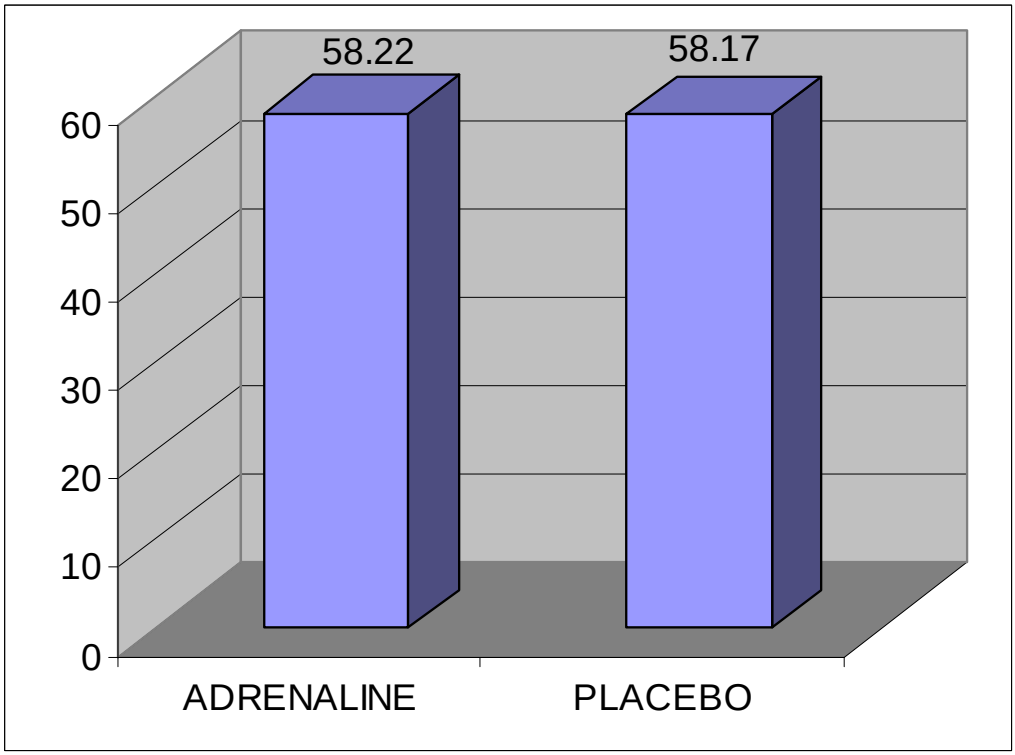


The mean age of both males and females did not grossly differ among study and placebo group as evidenced by the data above.

WEIGHT DISTRIBUTION AMONG MEMBERS IN STUDY AND PLACEBO GROUP

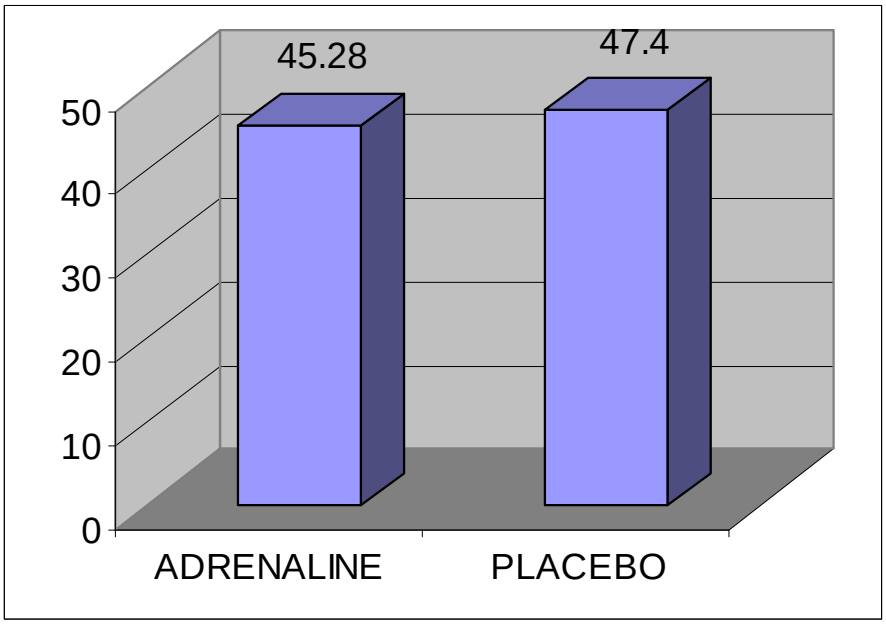
MALE

DETAIL	ADRENALINE	PLACEBO
(SD ; RANGE) WEIGHT (KG)	58.22 (4.94 ; 48-66)	58.17 (5.04; 50-70)



FEMALE

DETAIL	ADRENALINE	PLACEBO
(SD ; RANGE)	45.28	47.4
WEIGHT (KG)	(5.30 ; 38 - 54)	47.4 (5.36; 28-54)

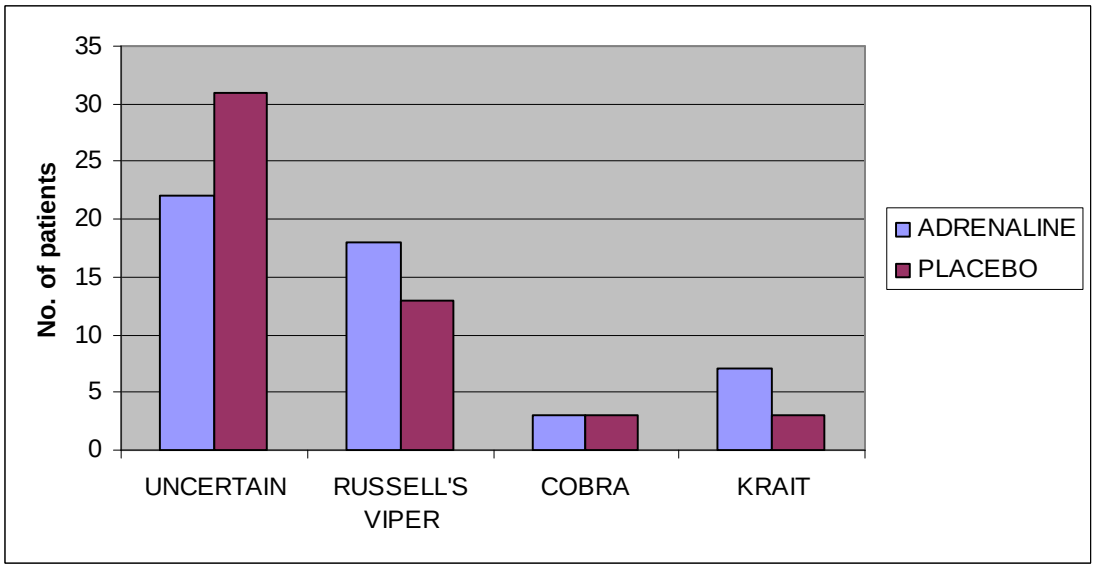


The data shows no significant difference in the mean weight among study and placebo group in both sexes.

SPECIES OF SNAKES

COMPARISON BETWEEN STUDY AND PLACEBO GROUP

DETAIL	ADRENALINE	PLACEBO
UNCERTAIN	22	31
RUSSELL'S VIPER	18	13
COBRA	3	3
KRAIT	7	3



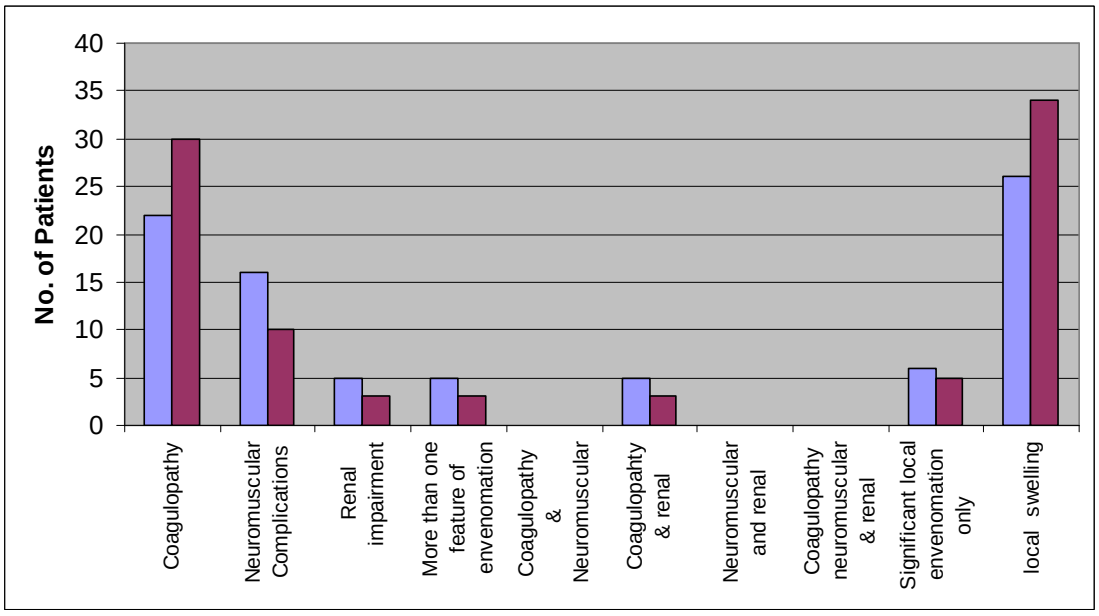
In 22 out of 50 patients among study group and 31 out of 50 patients among placebo group the snake could not be caught and thus remained unidentified. 18 snake bites in study group and 13 in placebo group were due to Russell's viper. Cobra and Krait bites were relatively rare as evidenced by the data.

SYSTEMIC ENVENOMATION : COMPARISON BETWEEN STUDY AND PLACEBO GROUP

Coagulopathy	22	30
Neuromuscular Complications	16	10
Renal impairment	5	3

More than one feature of envenomation	**5**	**3**
Coagulopathy & Neuromuscular	0	0
Coagulopathy & renal	5	3
Neuromuscular and renal	0	0
Coagulopathy neuromuscular & renal	0	0

Significant local envenomation only	6	5
Local swelling	26	34



A good proportion of patients - 22 in study group and 30 in placebo group developed coagulopathy. Neuromuscular complications were seen in 16 and 10 patients in study and placebo groups respectively where as renal impairment was seen in 5 patients in study group and 3 in placebo group.

Combinations of systemic envenomation per se was rare. 5 patients in study group and 3 patients in placebo group developed features of both coagulopathy and acute renal failure.

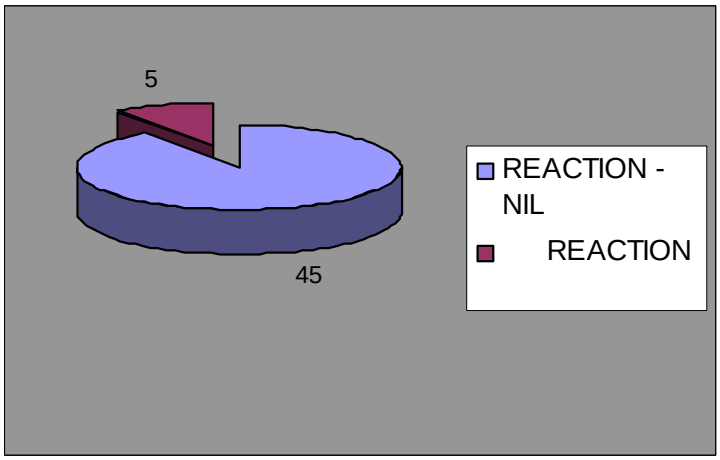
A high proportion of patients in both study and placebo groups developed local swelling. This was found to be 52% (26 patients) and 68% (34 patients) respectively. 6 patients in study group and 5 in placebo group had significant local envenomation which was cellulitis extending to more than half of the bitten limb. None of these patients had necrosis.

ACUTE ADVERSE REACTIONS TO ANTIVENOM SERUM TO PATIENTS BITTEN BY SNAKES, ACCORDING TO PRE TREATMENT (ADRENALINE OR PLACEBO)

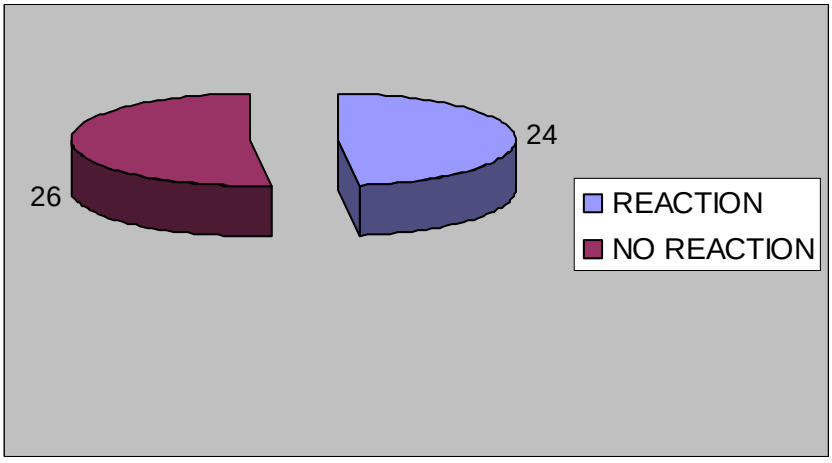
DETAIL	ADRENALINE (n=50)	PLACEBO (n=50)	RELATIVE RISK	P VALUE
NO (%) OF REACTION TO SERUM	5	24	0.21	.00005

TABLE - A

ADRENALINE



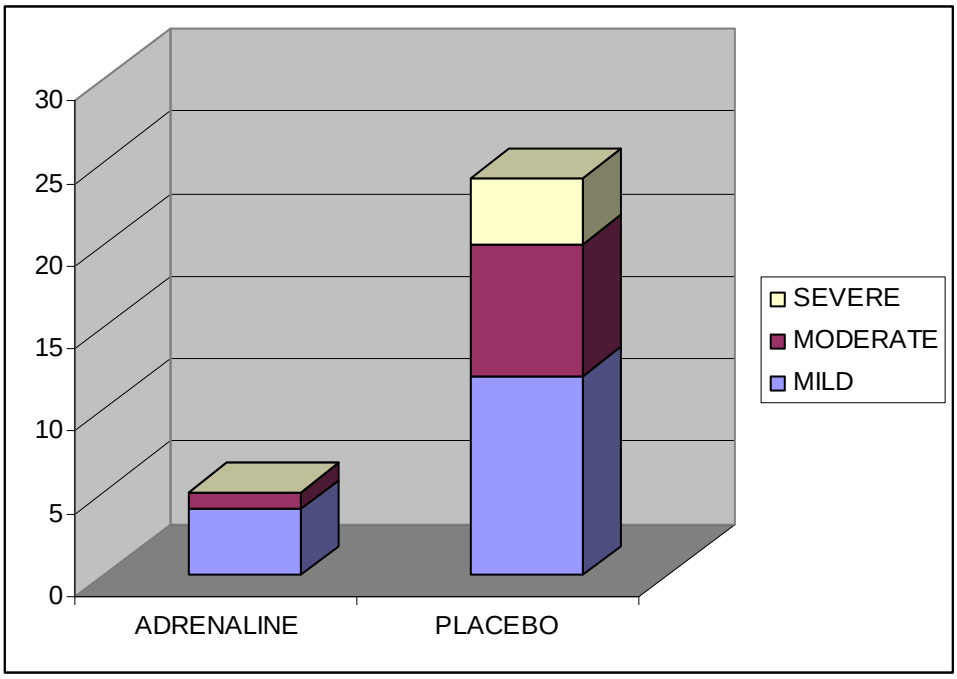
PLACEBO



PERCENTAGE OF REACTIONS ACCORDING TO SEVERITY

% OF REACTIONS ACCORDING TO SEVERITY	ADRENALINE n=50	PLACEBO (n=50)	RELATIVE RISK	P VALUE
MILD	4	12	0.67	.03
MODERATE	1	8	0.125	.01
SEVERE	0	4	0	.03

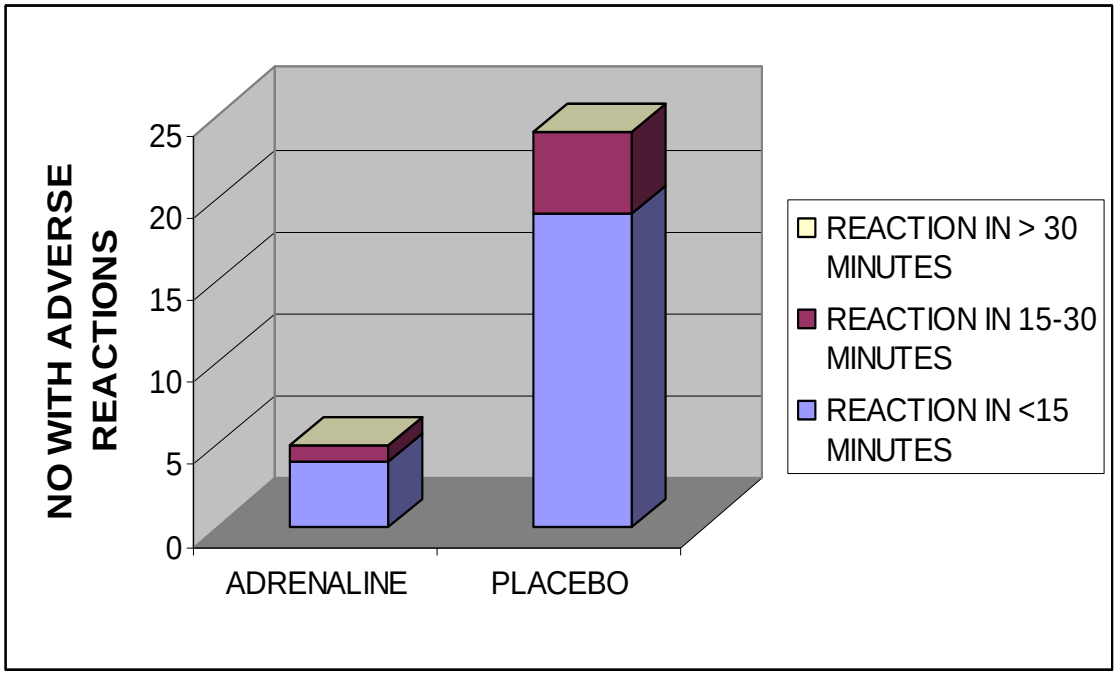
TABLE - B



None of the study patients died. Table A shows the incidence of acute adverse reactions to antivenom serum. There was a highly significant reduction of acute adverse events in the adrenaline group. Significant reductions in acute adverse reactions to the serum were also seen in adrenaline group for each category of mild, moderate and severe reaction. (P value .03, .01, .03 respectively) See Table B.

TIMING OF ADVERSE REACTIONS TO SERUM (MIN)

TIMING OF ADVERSE REACTIONS TO SERUM (MIN)	ADRENALINE	PLACEBO
<15	4	19
15-30	1	5
>30	0	0



Of the total 5 patients in study group, who developed reaction, 4 developed it within 15 minutes and 1 between 15 to 30 minutes. Of the total 24 patients who developed reaction in placebo group 19 developed it within 15 minutes while 5 patients developed it between 15 to 30 minutes. None of the patients, both in study and placebo group developed reaction after 30 minutes of starting the antivenin.

SIDE EFFECTS OF ADRENALINE

In none of the patients who received adrenaline or placebo had blood pressure over 160/100mm Hg nor did any experience neurological deficit suggestive of a cerebrovascular accident during monitoring. Two patients who received adrenaline and seven who received placebo developed sinus tachycardia. No patient developed any other arrhythmia. Transient drowsiness was observed in patients in the adrenaline group and in the placebo group. These were probably the effects of premedication (all patients had other features of a moderate or severe acute adverse reaction to the serum).

DISCUSSION

DISCUSSION

There is no clear scientific evidence or uniform policy for the use of premedication to prevent acute adverse reactions to antivenom serum. Among the drugs used, hydrocortisone and antihistamines, although probably of little value, seem to be the most preferred. Adrenaline is used only in a few centres[47]. (In a restrospective analysis of the use of premedication before treatment with antivenom serum for snake bite in Australia, adrenaline, steroids and anti histamines used in different combinations were found to reduce adverse reactions to the serum from 12.5% to 3%. Although the data did not differentiate between effects of individual drugs, the most effective premedication in the combinations seemed to be adrenaline.

A major concern regarding the use of adrenaline as premedication is the potential risk of intracerebral haemorrhage; a result of the combination of the ability of certain snake venoms to cause coagulopathy and the risk of hypertension with the use of adrenaline. This has led to a reluctance to use adrenaline. Few studies have analysed the risk of cerebral haemorrhage after use of

adrenaline. Of seven cases of fatal intracerebral haemorrhage after snake bite documented in Australia, only three patients had received adrenaline as premedication making the evidence incriminating adrenaline as the cause of cerebral haemorrhage weak [50]. Fears of development of hypertension after low dose adrenaline also seem unfounded. In a study by Heilborn et al, eight patients who received. 5 mg adrenaline subcutaneously showed only transient and probably insignificant rises in systolic blood pressure, while diastolic blood pressure decreased[16].

This study is a prospective randomized, placebo controlled trial to investigate the efficacy and safety of adrenaline as prophylaxis against acute adverse reactions to antivenom. Pretreatment with a small dose of subcutaneous adrenaline significantly reduced the incidence of acute adverse reactions to polyvalent antivenom serum. Adrenaline is cheap and easy to use. No significant adverse effects attributable to adrenaline was encountered during the study; there were no cases of acute neurological deficit suggestive of cerebrovascular accidents or patients in whom blood pressure rose significantly. It must be pointed out, however that patients who were potentially at high risk for use of adrenaline were excluded from the study and results regarding its safety should be viewed in this

context. Nevertheless, the benefits of this treatment seem to outweigh potential risks. The use of low dose subcutaneous adrenaline as a prophylactic measure to prevent acute adverse reactions to antivenom can be recommended in patients who have no contraindications for its use.

Studies by Premawardhena. P et al (1999)[34], the first of its kind, has given similar results. Regarding reactions to serum, P value was found to be 0.0002 while in our study it is 0.00005. Both being statistically very significant.

In the Srilankan study, P value for mild, moderate and severe reactions were found to be 0.05, 0.04 and 0.04 respectively. In our study it was .03, .01 and .03 respectively; all the values being statistically significant; thus proving the benefits of prophylactic adrenaline in preventing acute adverse effects to ASV.

Regarding the timing of the reaction, in Srilankan study, 5 out of 6 in study group and 19 out of 21 in placebo group developed reactions within 15 minutes of starting ASV, while in our study the figures were 4 out of 5 and 19 out of 24 respectively.

In the Srilankan study, 1 out of 6 in study group and 2 out of 21 in the placebo group developed reaction between 15 to 30 minutes while in our study, 1out of 5 in the study group and 5 out of 24 in the placebo group developed reactions in this time period.

None of the patients in either the study or the placebo group in both the Srilankan and our study developed reactions to ASV beyond 30 minutes of starting the drip.

In both the studies, there was no statistically significant difference among any variables between the study and placebo group.

CONCLUSION

CONCLUSION

1. Antivenom serum is the only effective treatment for envenomation after snake bite.

2. Acute adverse reactions to the serum are common and include anaphylactic shock.

3. Acute adverse reactions almost never occur beyond 30 minutes of starting ASV drip.

4. The Prophylactic use of 1:1000 adrenaline in a dose of 0.25 ml given subcutaneously immediately before the infusion of antivenom serum significantly reduces the risk of acute adverse reactions.

5. Significant side effects attributable to adrenaline almost never occur on giving prophylactic adrenaline to prevent adverse reactions to antivenom serum.

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PROFORMA

A	P

NAME : **AGE :** **SEX :** **IP NO :**

ADDRESS :

OCCUPATION : **WEIGHT :**

SPECIES OF SNAKE : UNCERTAIN :

VIPER :

COBRA :

KRAIT :

FIRST AID BEFORE ADMISSION : RECEIVED / NOT RECEIVED

MEAN DELAY IN ADMISSION TO HOSPITAL :

CONTRAINDICATIONS TO STUDY :

AGE <12 YRS

AGE>70 YRS

RECEIVED ANTISERA

RECEIVED ANTISERA IN THE PAST :

ENVENOMATION

A/R TO ADRENALINE

ATOPY

WHEEZING

HYPERTENSION

IHD

TIA

STROKE

UNEXPLAINED FOCAL NEUROLOGICAL SIGNS

PRIOR TREATMENT OTHER THAN FIRST AID

SYSTEMIC ENVENOMATION

	BT	
COAGULOPATHY :	CT	

NEUROMUSCULAR :

RENAL :

CELLULITIS

SEVERE LOCAL SWELLING :

ASV REACTION

MILD	MODERATE	SEVERE
PRURITIS	EXTENSIVE URTICARIA	PULMONARY OEDEMA:
SKIN RASH	FACIAL OEDEMA	BRONCHOSPASM WITH
URTICARIA	BRONCHOSPASM	CYANOSIS
FEVER	WITHOUT CYANOSIS	STRIDOR
RIGOR		SHOCK
NAUSEA		
VOMITING		

A : Adrenaline group

P : Placebo group

	BEFORE ASV	DURING / AFTER ASV
BP :		
ECG :		

PROFORMA AND

MASTER CHART

MASTER CHART

Sl. No.	Name	Age	Sex	IP No.	ASV Vials	DOA	WT Kg	Species of Snake *	C	CG	R	NP	React	Timing	Severity
1.	Paramasivam	25	M	948009	10	06-07-07	60	Uncertain	C	+	-	-	R	<15	Mild
2.	Arokyadas	43	M	947608	10	06-07-07	58	Russel	C	+	-	-	R	<15	Mod
3.	Ilayakumar	31	M	948046	10	07-07-07	63	Russel	C	+	+	-			
4.	Chellakannu	47	M	948186	10	08-07-07	56	Uncertain	C	+	-	-	R	<15	Severe
5.	Nagarajan	62	M	948408	10	10-07-07	52	Uncertain	C	+	-	-			
6.	Ambika	22	F	948738	10	13-07-07	50	Uncertain	-	-	-	+			
7.	Suresh	27	M	948620	10	12-07-07	66	Russel	S	+	+	-			
8.	Chinnayyan	40	M	948825	10	14-07-07	56	Cobra	-	-	-	+			
9.	Ponni	40	F	948859	10	14-07-07	54	Uncertain	C	+	-	-			
10.	Selvaraj	45	M	949472	10	19-07-07	58	Uncertain	C	-	-	-	R	15-30	Mild
11.	Sasikumar	25	M	949714	10	21-07-07	65	Uncertain	-	-	-	+			
12.	Chinnayya	33	M	950170	10	24-07-07	68	Russel	C	-	-	-			
13.	Kalimuthu	45	M	950061	10	24-07-07	54	Russel	C	-	-	-			
14.	Mathi	48	M	950390	10	25-07-07	56	Cobra	-	-	-	+			

Sl. No.	Name	Age	Sex	IP No.	ASV Vials	DOA	WT Kg	Species of Snake *	C	CG	R	NP	React	Timing	Severity
15.	Perumal	50	M	950385	10	26-07-07	58	Russel	C	+	-	-			
16.	Anthonysamy	25	M	950375	10	26-07-07	70	Uncertain	-	+	-	-	R	<15	Mild
17.	Anbalagan	57	M	950533	10	27-07-07	58	Russel	C	+	-	-	R	<15	Mild
18.	Rajasekar	21	M	951087	10	01-08-07	58	Uncertain	S	+	+	-			
19.	Sivalingam	40	M	951087	10	01-08-07	60	Uncertain	-	-	-	-			
20.	Arulsamy	37	M	951093	10	03-08-07	64	Russel	C	+	-	-	R	<15	Mild
21.	Nagaraj	50	M	951302	10	03-08-07	58	Cobra	-	-	-	+			
22.	Sakthivel	17	M	951330	10	05-08-07	50	Russel	C	+	-	-			
23.	Segamelam	60	M	951583	10	06-08-07	52	Uncertain	-	-	-	+			
24.	Thangavelu	60	M	951678	10	06-08-07	58	Russel	C	+	-	-	R	<15	mild
25.	Murugan	32	M	951689	10	07-08-07	52	Russel	C	+	+	-			
26.	Balayya	35	M	951811	10	08-08-07	60	Uncertain	-	+	-	-			
27.	Kathalingam	26	M	951928	10	08-08-07	66	Uncertain	S	+	+	-			
28.	Divyaraj	37	M	951983	10	09-08-07	64	Uncertain	C	+	-	-			
29.	Krishnamoorthy	48	M	952232	10	01-08-07	58	Cobra	-	-	-	+			

Sl. No.	Name	Age	Sex	IP No.	ASV Vials	DOA	WT Kg	Species of Snake *	C	CG	R	NP	React	Timing	Severity
30.	Govindaraj	45	M	952377	10	12-08-07	62	Uncertain	C	+	-	-			
31.	Sumathi	35	F	951480	10	04-08-07	51	Russel	C	-	-	-	R	<15	mod
32.	Nandhini	14	F	952333	10	12-08-07	28	Russel	C	+	-	-			
33.	Rengaraj	22	M	942354	10	12-08-07	64	Krait	-	-	-	+			
34.	Samuthram	30	M	952761	10	16-08-07	60	Uncertain	C	-	-	-	R	<15	severe
35.	Rani	24	F	952529	10	14-08-07	46	Russel	C	+	-	-			
36.	Vairam	47	F	952550	10	14-08-07	48	Russel	C	+	-	-			
37.	Veeramani	38	M	952819	10	16-08-07	62	Uncertain	S	+	-	-			
38.	Rajanagam	45	M	952846	10	16-08-07	64	Russel	C	-	-	-	R	<15	mild
39.	Govindaraj	45	M	953130	10	19-08-07	58	Russel	C	+	-	-			
40.	Arjunan	45	M	953140	10	19-08-07	64	Krait	-	-	-	+	R	15-30	mod
41.	Lakshmanan	36	M	953277	10	19-08-07	62	Uncertain	S	+	-	-			
42.	Sasikala	32	F	953175	10	20-08-07	50	Krait	C	-	-	+			
43.	Nabeesabeevi	20	F	953310	10	21-08-07	42	Russel	C	+	-	-			
44.	Samiammal	55	F	953610	10	23-08-07	52	Uncertain	C	-	-	-	R	15-30	mild

Sl. No.	Name	Age	Sex	IP No.	ASV Vials	DOA	WT Kg	Species of Snake *	C	CG	R	NP	React	Timing	Severity
45.	Kalaiyanarasan	25	M	953900	10	25-08-07	66	Krait	C	-	-	+			
46.	Saroja	45	F	954080	10	26-08-07	54	Uncertain	C	+	-	-			
47.	Sumathy	25	F	954045	10	27-08-07	48	Uncertain	C	-	-	-			
48.	Malathy	28	F	954192	10	27-08-07	52	Uncertain	C	-	-	-	R	<15	mod
49.	Kalyani	43	F	954196	10	27-08-07	54	Russel	C	-	-	-			
50.	Kulandaiy yamal	55	F	954359	10	29-08-07	52	Uncertain	C	+	-	-			
51.	Chandran	60	M	954471	10	30-08-07	60	Uncertain	C	-	-	-			
52.	Ramachardran	60	M	954483	10	30-08-07	52	Uncertain	C	+	+	-			
53.	Saroja	30	F	954786	10	01-09-07	38	Russel	C	+	-	-			
54.	Shanmugam	30	M	955085	10	03-09-07	54	Uncertain	-	-	-	+	R	15-30	mild
55.	Karupayyan	50	M	955192	10	04-09-07	50	Uncertain	C	-	-	+			
56.	Sundar	38	M	955261	10	04-09-07	56	Uncertain	S	+	-	-	R	<15	mild
57.	Pusphalatha	29	F	955756	10	04-09-07	38	Uncertain	-	+	-	-			
58.	Sandaradevi	45	F	955188	10	04-09-07	42	Uncertain	S	+	-	-	R	<15	mod
59.	Dhanalakshmi	40	F	955241	10	04-09-07	41	Russel	C	+	-	-			

Sl. No.	Name	Age	Sex	IP No.	ASV Vials	DOA	WT Kg	Species of Snake *	C	CG	R	NP	React	Timing	Severity
60.	Kaliyammal	40	F	955346	10	05-09-07	47	Krait	-	-	-	+			
61.	Manoharan	23	M	955117	10	05-09-07	60	Uncertain	-	-	-	+			
62.	Muniyatha	45	F	955722	10	08-09-07	48	Uncertain	C	-	-	-			
63.	Apoorvam	45	F	955749	10	08-09-07	44	Russel	C	-	-	-	R	15-30	mild
64.	Reetamary	28	F	955773	10	09-09-07	45	Russel	C	+	-	-			
65.	Susheela	21	F	955950	10	10-09-07	40	Uncertain	-	-	-	+			
66.	Indirani	35	F	956041	10	11-09-07	51	Uncertain	C	+	-	-	R	<15	mild
67.	Sumathy	38	F	956127	10	12.09.07	40	Krait	-	-	-	+			
68.	Krishnamoorthy	40	M	955929	10	10.09.07	52	Uncertain	C	+	-	-	R	<15	mod
69.	Sekar	30	M	955943	10	10.09.07	60	Uncertain	-	-	-	+			
70.	Arumainesan	55	M	956347	10	13.09.07	52	Uncertain	S	+	-	-			
71.	Rani	40	F	956122	10	12.09.07	48	Uncertain	-	+	-	-			
72.	Yamuna	25	F	956264	10	13.09.07	46	Russel	C	+	-	-	R	<15	severe
73.	Sahayarani	38	F	956258	10	13.09.07	52	Russel	C	-	-	-			
74.	Elizabeth	48	F	956247	10	13.09.07	50	Cobra	-	-	-	+			

Sl. No.	Name	Age	Sex	IP No.	ASV Vials	DOA	WT Kg	Species of Snake *	C	CG	R	NP	React	Timing	Severity
75.	Kavitha	19	F	956390	10	14.09.07	40	Krait	-	+	-	-			
76.	Veerammal	40	F	956433	10	14.09.07	44	Russel	C	+	-	-	R	<15	mild
77.	Rajagopal	50	M	956588	10	15.09.07	54	Krait	-	-	-	+			
78.	Jayachitra	25	F	957027	10	16.09.07	46	Russel	C	+	-	-	R	15-30	mild
79.	Anandan	35	M	957112	10	17.09.07	56	Uncertain	C	-	-	-			
80.	Muthukannu	40	F	957144	10	17.09.07	48	Uncertain	C	-	-	+			
81.	Kaliyan	65	M	957386	10	18.09.07	48	Krait	-	-	-	+			
82.	Vadivel	65	M	957410	10	18.09.07	52	Uncertain	C	+	-	-	R	<15	Mild
83.	Palanisamy	19	M	957496	10	19.09.07	54	Russel	C	-	-	-			
84.	Poomalai	32	M	957552	10	19.09.07	62	Uncertain	-	-	-	+	R	<15	Mod
85.	Kamaraj	48	M	957537	10	19.09.07	48	Russel	C	+	+	-	R	<15	Mild
86.	Kumar	45	M	957687	10	20.09.07	54	Uncertain	S	+	-	-			
87.	Mala	25	F	957701	10	21.09.07	40	Uncertain	S	+	-	-			
88.	Thirugnanam	60	M	957745	10	21.09.07	56	Russel	C	+	-	-	R	<15	Mod
89.	Kavitha	25	F	957914	10	22.09.07	44	Cobra	-	-	-	+			

Sl. No.	Name	Age	Sex	IP No.	ASV Vials	DOA	WT Kg	Species of Snake *	C	CG	R	NP	React	Timing	Severity
90.	Palani	30	M	957963	10	23.09.07	62	Uncertain	C	+	-	-			
91.	Govindaraj	40	M	1958207	10	24.09.07	56	Uncertain	C	-	-	-			
92.	Indiragandhi	35	F	958349	10	25.09.07	49	Uncertain	C	-	-	-	R	<15	severe
93.	Shanmughanathan	30	M	958239	10	25.09.07	60	Krait	-	-	-	+			
94.	Sakkararathi	42	M	958367	10	25.09.07	63	Uncertain	-	+	-	-			
95.	Chinnaiyyan	40	M	958474	10	26.09.07	59	Uncertain	-	-	-	+			
96.	Mudiyappan	53	M	958631	10	27.09.07	52	Uncertain	C	+	-	-	R	<15	mod
97.	Sarasu	40	F	958495	10	26.09.07	49	Russel	S	+	-	-			
98.	Mariyayi	25	F	958781	10	28.09.07	46	Uncertain	C	+	+	-			
99.	Ramasamy	52	M	958873	10	29.09.07	54	Uncertain	C	+	-	-			
100.	Dhanapal	50	M	958940	10	30.09.07	52	Uncertain	C	-	-	-			

Sl. No. : SERIAL NO.

C : CELLULITIS

S : SEVERE CELLULITIS EXTENDING MORE THAN HALF OF THE LIMB

WT : WEIGHT IN KILOGRAMS

*SPECIES OF SNAKE DOCUMENTED ONLY IF THE SNAKE WAS BROUGHT BY THE ATTENDER

CG : Coagulopathy

R : Renal failure

NP : Neuroparalytic manifestations

React : Anaphylactic Reaction

Timing : in Minutes

Mod : Moderate

☐ Adrenaline

☐ Placebo